TRILACICLIB (G1T28), A CYCLIN DEPENDENT KINASE 4/6 INHIBITOR, IN COMBINATION WITH TOPOTECAN FOR PREVIOUSLY TREATED SMALL CELL LUNG CANCER: PRELIMINARY RESULTS

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BACKGROUND

Chemotherapy-induced bone marrow and immune system toxicity causes significant acute and long-term consequences. Trilaciclib (G1T28) is an IV, short-acting CDK4/6 inhibitor in development to preserve hematopoietic stem cell (HSC) and immune system function during chemotherapy in patients with CDK4/6-independent cancers such as small cell lung cancer (SCLC). HSCs and progenitors are dependent upon CDK4/6 for proliferation, and preclinical models demonstrated that transient trilaciclib-induced G1 cell cycle arrest renders them resistant to chemotherapy cytotoxicity, allowing faster hematopoietic recovery, preservation of long-term HSC and immune system function, and enhancement of anti-tumor activity.

Topotecan is indicated for the treatment of patients with SCLC with platinum-sensitive disease who progressed at least 60 days after completion of first-line chemotherapy. In the randomized Phase 3 trial of topotecan versus cyclophosphamide, doxorubicin, vincristine (CAV), the overall response rate (ORR) was 24%, clinical benefit rate (CBR) was 43.9%, median progression free survival (PFS) was 3.1 months, and median overall survival (OS) was 5.8 months[1]. Similar efficacy was seen in a more recent Phase 3 study using topotecan as the standard of care, where the ORR was 16.9%, CBR was 61.5%, median PFS was 3.5 months, and median OS was 7.5 months[2]. In subgroup analysis by sensitivity to first line therapy, patients with sensitive disease had an ORR of 23.1%, median PFS was 4.3 months, and median OS was 9.9 months. However, in patients with refractory disease the ORR was 9.4%, median PFS was 2.8 months and median OS was 5.7 months. Despite improvement in disease symptoms, patients experience severe myelosuppression, which limits topotecan dose intensity (Tables 1 and 2)[1,2].

TABLE 1. HISTORICAL HEMATOLOGIC GRADE 3/4 ADVERSE DRUG REACTIONS IN SCLC PATIENTS RECEIVING TOPOTECAN

	Von Pawel 1999[1]				Von Pawel 2014[2]
	Patients (n=104)		Cycles (n=439-441)		Patients (n=197)
Grade	3/4 n(%)	4 n(%)	3/4 n(%)	4 n(%)	3/4 n(%)
Neutropenia	92 (88.5)	73 (70.2)	303 (69)	166 (37.8)	106 (53.8)
Thrombocytopenia	60 (57.6)	30 (28.8)	126 (28.6)	43 (9.8)	107 (54.3)
Anemia	44 (42.3)	3 (2.9)	78 (17.7)	5 (1.1)	60 (30.5)

TABLE 2. HISTORICAL HEMATOLOGIC COMPLICATIONS IN SCLC PATIENTS RECEIVING TOPOTECAN

	Von Pawel 1999[1]		Von Pawel 2014[2]
	Patients (n=104)	Cycles (n=439-441)	Patients (n=197)
	n(%)	n(%)	n(%)
G-CSF	NR	25 (5.6)	NR ‡
Erythropoietin	NR	NR	NR ‡
RBC Transfusions	(52.3)	(24.7)	104* (52.8)
Plt Transfusions	(19.5)	(5.8)	
Febrile Neutropenia	30 (28)	39 (8.7)	6 (3)
Sepsis	5 (4.7)	5 (1.1)	NR
Patients with ≥ 1 dose reductions	NR †	NR †	88 (44.7)
Patients with > 2 dose reductions	NR †	NR †	37 (18.8)

Abbreviations: NR, not reported; Plt, platelet; RBC, red blood cell

* Number of transfusions were reported but not broken out by RBC or platelet.

‡ Protocol was amended to mandate the use of prophylactic hematopoietic growth factors in all cycles for all patients.

† The target dose of topotecan was maintained in 76% of patients and 7.1% of topotecan cycles were delayed beyond one week.

REFERENCES

1. von Pawel J(1), Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, Stewart DJ, Clark PI, Palmer MC, Depierre A, Carmichael J, Krebs JB, Ross G, Lane SR, Gralla R. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol.* 1999 Feb;17(2):658-67.

2. von Pawel J, Jotte R, Spigel DR, O'Brien ME, Socinski MA, Mezger J, Steins M, Bosquée L, Bubis J, Nackaerts K, Trigo JM, Clingan P, Schütte W, Lorigan P, Reck M, Domine M, Shepherd FA, Li S, Renschler MF. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol.* 2014 Dec 10;32(35):4012-9.

OBJECTIVES

Assess the dose limiting toxicities (DLTs), safety and tolerability, hematological profile, pharmacokinetics (PK) and anti-tumor activity of trilaciclib in combination with topotecan (NCT02514447).

METHODS

STUDY DESIGN

- Multicenter Phase 1b/2a study
- Part 1 is open-label, dose-finding; Part 2 is randomized (2:1), double blind, in 60 patients
- Trilaciclib was administered at a starting dose of 200 mg/m^2 IV prior to topotecan
- Topotecan was administered at a starting dose of 1.5 mg/m^2 on days 1-5 every 21 days

SELECTED INCLUSION CRITERIA

1. Age ≥ 18 years
2. Unequivocally confirmed diagnosis of SCLC by histology or cytology
3. Progression during or after prior 1st- or 2nd-line chemotherapy
4. At least 1 target lesion that is measurable by RECIST, version 1.1
5. Organ Function: Hgb ≥ 9 g/dL, ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, creatinine ≤ 1.5 mg/dL and GFR of ≥ 60 mL/min, bilirubin ≤ 1.5 x ULN, AST and ALT ≤ 2.5 x ULN or ≤ 5 x ULN in the presence of liver metastases, serum albumin ≥ 3 g/dL
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

SELECTED EXCLUSION CRITERIA

1. History of topotecan treatment for SCLC
2. Presence of brain metastases requiring immediate treatment with radiation or steroids
3. Concurrent radiotherapy to any site or radiotherapy within 2 weeks
4. Significant cardiac or cerebrovascular disease
5. Other uncontrolled serious chronic disease or conditions
6. Receipt of any systemic chemotherapy regimen within 4 weeks prior to enrollment or an investigational medication within 2 weeks prior to enrollment

ASSESSMENTS

- Patients continuously assessed for safety
- Tumor response after every even cycle until disease progression and for patients who did not progress on treatment every 60 days ± 7 until disease progression
- Hematology assessments at screening, days 1, 5, 10, 12, and 15 of each cycle, day 22 of the last cycle, and the Post-Treatment Visit
- Trilaciclib and topotecan plasma PK concentrations were quantified on days 1 and 4 of cycle 1

DEFINITION OF DOSE-LIMITING TOXICITIES (APPLICABLE TO CYCLE 1 OF PART 1 ONLY)

- Absolute neutrophil count (ANC) < 0.5 × 10^9/L lasting for ≥ 7 days
- ≥ Grade 3 neutropenic infection/febrile neutropenia
- Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia with bleeding
- Unable to start Cycle 2 due to a lack of recovery to an ANC ≥1.5 × 10^9/L and platelet count ≥ 100 × 10^9/L; a delay of up to 1 week from the scheduled start of Cycle 2 is allowed for recovery of ANC and platelet count, and is not considered a DLT (revised by the Safety Monitoring Committee from the original criteria which did not allow a one week recovery)
- ≥ Grade 3 nonhematologic drug-related toxicity (nausea, vomiting, and diarrhea failing maximal medical management; fatigue lasting for > 72 hours)

RESULTS

TABLE 3. BASELINE PATIENT AND DISEASE CHARACTERISTICS FOR ENROLLED PATIENTS

Patients enrolled	29
Age, years median (range)	64 (46-79)
Gender, n (%)	
Male	19 (66)
Female	10 (34)
Race, n (%)	
White	26 (90)
African-American	3 (10)
Ethnicity, n (%)	
Not Hispanic or Latino	29 (100)
Hispanic or Latino	0
ECOG Performance Status, n (%)	
0	9 (31)
1	17 (59)
2	3 (10)
Known Brain Metastasis, n (%)	
No	26 (90)
Yes	3 (10)
Platinum Sensitivity, n (%)	
Sensitive	18 (62)
Resistant	9 (31)
Unknown	2 (7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group

TABLE 4. COHORT DOSE LEVELS

Cohort	Topotecan Dose (mg/m^2)	Trilaciclib Dose (mg/m^2)
1	1.5	200
2	1.25	200
3	0.75	200
4 & 6	0.75	240
5	0.75	280
7	1.0	240

TABLE 5. SUMMARY OF TOPOTECAN EXPOSURE

Topotecan Dose (mg/m^2)	Number of Cycles
1.5	3
1.25	7
1.0	12
0.75	85
0.7	2
0.6	6
TOTAL	115

RESULTS

TABLE 6. SUMMARY OF PLASMA TRILACICLIB AND TOPOTECAN PHARMACOKINETIC PARAMETERS

	Statistic	Cmax (ng/mL)	t1/2 (h)	$AUC_{0\text{-}24}$ (h*ng/mL)	Day 4 $AUC_{0\text{-}24}$ (h*ng/mL)	CL (L/min/m^2)	Vss (L/m^2)
Trilaciclib							
200 mg/m^2 (n=9)	Mean min-max	1220 660-2550	7.11 5.60-9.20	2220 1610-2870	2550 1720-3410	86.3 66.9-118	608 333-873
240 mg/m^2 (n=9)	Mean min-max	698 410-1550	7.22 5.27-10.5	2240 1510-2690	2450 1740-3560	103 79.9-149	803 637-1090
280 mg/m^2 (n=9)	Mean min-max	1250 679-2280	7.63 6.75-9.53	3290 2390-4490	4750 2910-6690	82.0 57.8-111	688 487-916
	Statistic	**Cmax (ng/mL)**	**t1/2 (h)**	**AUCinf (h*ng/mL)**	**AUCx5 (min*nM)**	**CL (L/min/m^2)**	**Vss (L/m^2)**
Topotecan							
0.75 mg/m^2 (n=19)	Mean min-max	22.7 13.8-42.5	4.06 1.96-5.99	82.8 41.4-120	54300 27100-78600	0.166 0.104-0.302	47.6 31.3-65.8
1 mg/m^2 (n=2)	Mean min-max	34.3 15.7-52.8	5.12 4.76-5.48	141 90.5-192	92600 59300-126000	0.135 0.0867-0.184	54.7 33.2-76.1
1.25 mg/m^2 (n=3)	Mean min-max	63.7 39.3-94.1	4.93 4.78-5.09	180 123-254	118000 80400-166000	0.127 0.0820-0.170	40.2 27.9-53.0
1.5 mg/m^2 (n=2)	Mean min-max	69.5 40.2-98.8	4.33 4.11-4.56	152 132-171	99400 86600-112000	0.167 0.146-0.189	43.0 34.9-51.2
Topotecan Historical Control*							
1.5 mg/m^2	Mean min-max				48127 28735-84866	0.340 0.193-0.570	

* Historical mean clearance values from 6 published reports were used to generate a range of AUCx5 values (Saltz et al. *J Natl Cancer Inst.* 1993; Van Warmerdam et al. *Cancer Chemother Pharmacol.* 1995; O'Reilly et al. *J Clin Oncol.* 1996; Gallo et al. *J Clin Oncol.* 2000; Montazeri et al. *Clin Cancer Res.* 2002; Mould et al. *Clin Pharmacol Ther.* 2002).

TABLE 7. GRADE 3/4 TREATMENT-RELATED ADVERSE EVENTS*

AE Term	Cohort 1 (n=2)		Cohort 2 (n=3)		Cohort 3 (n=4)		Cohorts 4&6 (n=8)		Cohort 5 (n=7)		Cohort 7 (n=5)		Total (n=29)	
	3/4	4	3/4	4	3/4	4	3/4	4	3/4	4	3/4	4	3/4	4
Anemia	2	0	1	0	2	0	0	0	1	0	2	0	8	0
Leukopenia	2	2	2	1	1	0	1	0	3	1	2	0	11	4
Neutropenia	2	2	2	2	1	1	3	0	2	1	3	1	13	7
Thrombocytopenia	2	2	2	1	3	2	0	0	3	2	1	0	11	7

*Grade 3/4 adverse events occurring in ≥ 10% of patients are shown. Toxicities were graded using NCI Common Terminology Criteria for Adverse Events, Version 4.03.

TABLE 8. SUMMARY OF DOSE LIMITING TOXICITIES

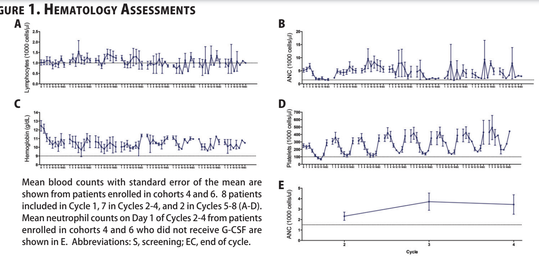
DLT Criteria	Cohort 1 (n=2)	Cohort 2 (n=3)	Cohort 3 (n=4)	Cohort 4&6 (n=8)	Cohort 5 ‡ (n=6)	Cohort 7* (n=3)
G4 Neutropenia for ≥ 7 days	2	2	--	--	--	1
G4 Thrombocytopenia	1	1	2	--	2	--
ANC < 1.5x10^9/L on Cycle 2 Day 1	--	--	--	4	1	2
% of patients with DLT per original criteria	100%	67%	50%	50%	33%	67%
% of patients with DLT per revised criteria	100%	67%	50%	0%	33%	33%

‡ 1 patient in cohort 5 was not evaluable for DLT and was replaced; *2 patients in cohort 7 are still in cycle 1 and are not evaluable for DLT.

TABLE 9. DOSE REDUCTION, DOSE DELAYS, GROWTH FACTOR USAGE, AND TRANSFUSIONS

	All Patients (n=29)	Cohorts 3-6 (n=19)	Cohorts 4&6 (n=8)	Cohort 7 (n=5)
Topotecan dose level(s)	0.75-1.5	0.75	0.75	1
Trilaciclib dose level(s)	200-280	200-280	240	240
Total cycles administered	115	76	39	7
Cycles delayed, n (%)	17 (15)	10 (13)	5 (13)	1 (14)
Patients with ≥ 1 dose delay, n (%)	13 (45)	9 (47)	5 (63)	1 (20)
Patients with ≥ 1 dose reduction, n (%)	8 (28)	3 (16)	0 (0)	0 (0)
Patients with ≥ 1 dose of erythropoietin, n (%)	4 (14)	1 (5)	1 (12.5)	0 (0)
Patients with ≥ 1 dose of G-CSF, n (%)	9 (31)	5 (26)	2 (25)	0 (0)
Patients with ≥ 1 transfusion, n (%)	8 (28)	4 (21)	0 (0)	1 (20)

FIGURE 1. HEMATOLOGY ASSESSMENTS



Mean blood counts with standard error of the mean are shown from patients enrolled in cohorts 4 and 6. 8 patients included in Cycle 1, 7 in Cycles 2-4, and 2 in Cycles 5-8 (A-D). Mean neutrophil counts on Day 1 of Cycles 2-4 from patients enrolled in cohorts 4 and 6 who did not receive G-CSF are shown in E. Abbreviations: S, screening; EC, end of cycle.

FIGURE 2. BEST CHANGE IN TUMOR SIZE FROM BASELINE

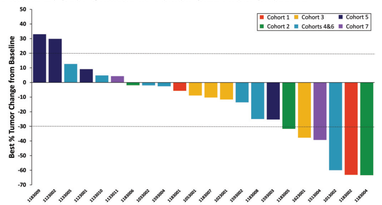


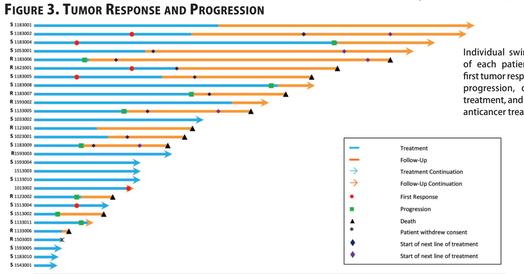
TABLE 10. TUMOR RESPONSE BY RECIST V1.1 IN EVALUABLE PATIENTS

	Overall (n=23)	Sensitive (n=15)	Resistant (n=7)
PR	6*	4	1
SD	12	8	4
PD	5	3	2
ORR	26%	27%	14%
CBR	78%	80%	71%

* 1st line platinum sensitivity was unknown for 1 patient with a PR.

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CBR, clinical benefit rate.

FIGURE 3. TUMOR RESPONSE AND PROGRESSION



Individual swimmer plots of each patient showing first tumor response, tumor progression, duration of treatment, and subsequent anticancer treatment.

CONCLUSIONS

- In this ongoing study, the combination of trilaciclib with topotecan is well tolerated, without any episodes of febrile neutropenia or treatment-related SAEs
- The most common adverse events were hematologic toxicities attributed to chemotherapy; in the setting of frequent hematologic monitoring, Grade 3/4 events recovered quickly, were associated with fewer topotecan dose delays/reductions and less growth factor usage and transfusions than those reported in the literature
- A pharmacologic drug-drug interaction resulting in reduced topotecan clearance and consequent increase in topotecan exposure was identified; however, exposures at a topotecan dose of 0.75 mg/m^2 with trilaciclib were comparable to those reported in the literature for 1.5 mg/m^2 topotecan alone
- Early anti-tumor results (ORR and CBR) are encouraging
- This novel approach, allowing the administration of chemotherapy with preservation of HSC and immune system function, could potentially improve treatment outcomes for patients with CDK4/6-independent tumors